REMARKS

Reconsideration of the above-identified application in view of the amendment above and the remarks below is respectfully requested.

No claims have been canceled or added in this paper. Claim 1 has been amended in this paper. Therefore, claims 1-15 are pending. Of these claims, claims 12-15 are withdrawn as being directed at a non-elected invention. Accordingly, claims 1-11 are under active consideration.

Claims 1-11 stand rejected under 35 U.S.C. 112, second paragraph. In support of the rejection, the Patent Office states the following:

> Claims 1-11 recite the limitation "the nucleic acid" in step d. There is insufficient antecedent basis for this limitation in the claim. This rejection can easily be overcome by amending the claim to recite, "the genomic DNA."

Without acquiescing in the propriety of the rejection, Applicant has amended claim 1. Accordingly, the rejection has been overcome and should be withdrawn.

Claims 1-6, 9 and 10 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010)." In support of the rejection, the Patent Office repeats its reasons of record and then states the following:

> The response of 6/1/2007 asserts that one of ordinary skill in the art would not have been motivated to substitute the DNMT1 of Pradhan for the methyl transferase of Lopez and such a motivation would render the method of Lopez unsatisfactory for its intended use. These arguments have been fully considered but are not found persuasive because the combination of Lopez and Pradhan would result in amplification of genomic DNA whereby the methylation pattern of the genomic DNA would be maintained. The Lopez teaches that methods of amplifying genomic DNA in the presence of methyltransferases were known. Further Pradhan teaches the importance of maintenance methylation and the importance of

DNMT1. The combination of Pradhan would thus render the instant claims obvious. The instant claims are drawn to the combinations of known methods, techniques and reagents to amplify and methylate genomic DNA. It would thus be obvious to substitute the DNMT1 for the methyl transferase of Lopez to maintain genomic methylation patterns as Pradhan teaches genomic methylation pattens are important in cancer and development.

The response of 6/1/2007 further asserts on pages 7 and 8, that the references do not teach or suggest the desirability of the propagating the methylation patterns other than to cite the importance in embryonic development, carcinogenesis and genetic disease. These arguments would appear to suggest that the claimed invention lacks utility, however the response further asserts that the method increases the accuracy of methylation detection assays. Lopez teaches, "It is an object of the present invention to provide a method utilizing a DNA methyltransferase in conjunction with a PCR amplicon so that a quick and accurate determination of nucleic acid variation can be determined." Thus the combination of Lopez and Pradhan would use known methods, techniques and reagents with a predictable chance of success accurately determine methylation patterns.

The response further asserts that value of the instantly claimed invention is that it increases the accuracy of restriction digests (which Lopez teaches) or bisulfite methylation assays. The instant claims do not require performing any steps of restriction digestion or bisulfite based assays, the reason response is asserting improved results. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., increased specificity of methylation assays) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The modification of Lopez in view of Pradhan would necessarily result increased accuracy of the assay as asserted in the response as the genomic DNA would be amplified with the genomic methylation pattern maintained.

Thus the instant claims are obvious in view of the teachings of Lopez and Pradhan.

Applicant respectfully traverses the subject rejection.

The present invention teaches a method for use in METHYLATION analysis. One main problem in methylation analysis is that PCR cannot be applied directly, as cytosine and methylcytosine show the same base pair behavior. As a consequence, the methylation information is lost after PCR. (During PCR, methylcytosines are converted to cytosines; consequently, a distinction between originally-methylated cytosines and unmethylated cytosines is not possible.)

Prior to the present invention, this problem had been addressed either by application of methylation-specific restriction enzymes or by application of bisulfite-conversion of DNA, but, in either case, PRIOR to amplification.

The present invention allows, for the first time, an amplification which retains the methylation status and, therefore, does not require a pre-treatment.

By contrast, Lopez et al. does not teach a method for use in methylation analysis and does not teach a methylation-retaining PCR technique. In fact, in the method described by Lopez et al., any methylation information initially present in the DNA is completely lost as a result of the Lopez technique.

More specifically, Lopez et al. teaches a method for genotyping and detection of polymorphism. In the first step, amplification is performed. Then, the amplificates are reacted with a methyltransferase and a labeled methyl-donor. If the amplificates contain recognition sequences for the methytransferase, the labels are introduced into the sequences. If the amplificates do not contain said recognition sequences (in other words, if the sequences are mutated), no labels are introduced. By comparative detection of the label, mutated and non-mutated sequences can be distinguished.

Lopez et al. does not teach a method suitable for methylation analysis. In contrast, Lopez et al. uses artificial methylation for the detection of mutations. The method of Lopez et al. is, in principle, not amenable to methylation analysis. This is because the first amplification step of the Lopez method erases all of the existing methylation information. Moreover, this erasure is a necessary step in the Lopez method since the methylation to be detected is not previously-existing methylation but artificially-introduced methylation.

In fact, it is only because, in accordance with Lopez, all methylated cytosines are converted to non-methylated cytosines in the first amplification step that all potential binding sites are thereafter available for the methyltransferase. In other words, if the Lopez method resulted in partially methylated DNA being generated, the method would not work reliably. This is because, if a label cannot be detected, this could then either be due to a mutation in the DNA or to a sequence already occupied by a natural (non-labeled) methylgroup.

In summary, Lopez et al. teaches a completely different problem with a completely different technology. Lopez et al. teaches performing PCR (thereby effectively erasing pre-existing methylations) and then methylating at specific positions using a methyltransferase that is sequence-specific. There would have been no reason to modify the Lopez method by replacing the methyltransferase of Lopez et al. with the DNMT1 of Pradhan et al. since, by the time that the DNA would have been contacted with the DNMT1 using the Lopez method, there would not have been a methylation pattern to maintain. Lopez et al. is not concerned with **maintaining** methylation in amplified DNA, but rather, in **introducing** methylation at sequence-specific sites in amplified DNA. Consequently, to the extent that the Patent Office argues in the outstanding Office Action that "the combination of Lopez and Pradhan would result in amplification of genomic DNA whereby the

methylation pattern of the genomic DNA would be maintained," Applicant respectfully disagrees because, as noted above, the Lopez method is predicated on **introducing** a methylation pattern into the DNA, not on **maintaining** a methylation pattern in the DNA.

As noted above, the Patent Office argues in the instant Office Action

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claim 7 stands rejected under 35 U.S.C. 103(a) "as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claim 1-6, 9, and 10 above, and further in view of Shatkin et al (US Patent 6312926)." In support of the rejection, the Patent Office repeats its reasons of record and then states the following:

> The response of 6/1/2007 asserts on page 8, that Shatkin et al does not cure all of the deficiencies of Lopez in view of Pradhan, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying by PCR genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

Applicant respectfully traverses the subject rejection. Claim 7 depends from claim 1. Claim 1 is patentable over the combination of Lopez et al. and Pradhan et al. for at least the reasons given above. Shatkin et al. fails to cure all of the deficiencies of Lopez et al. and Pradhan et al. with respect to claim 1. Therefore, based at least on its dependency from claim 1, claim 7 is patentable over the applied combination of Lopez et al., Pradhan et al. and Shatkin et al.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claim 8 stands rejected under 35 U.S.C. 103(a) "as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claims 1-6, 9, and 10 above, and further in view of Stemple et al (WO/2000/53805)." In support of the rejection, the Patent Office repeats its reasons of record and then states the following:

> The response of 6/1/2007 asserts on page 8, that Stemple et al does not cure all of the deficiencies of Lopez in view of Pradhan, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying by PCR genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

Applicant respectfully traverses the subject rejection. Claim 8 depends from claim 1. Claim 1 is patentable over the combination of Lopez et al. and Pradhan et al. for at least the reasons given above. Stemple et al. fails to cure all of the deficiencies of Lopez et al. and Pradhan et al. with respect to claim 1. Therefore, based at least on its dependency from claim 1, claim 8 is patentable over the applied combination of Lopez et al., Pradhan et al. and Stemple et al.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claim 11 stands rejected under 35 U.S.C. 103(a) "as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claims 1-6, 9 and 10 above, and further in view of Gonzalgo et al (US Patent 6251594)." In support of the rejection, the Patent Office repeats its reasons of record and then states the following:

> The response of 6/1/2007 asserts on page 9, that Gonzalgo et al does not cure all of the deficiencies of Lopez in view of Pradhan,

> as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying by PCR genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

Applicant respectfully traverses the subject rejection. Claim 11 depends from claim 1. Claim 1 is patentable over the combination of Lopez et al. and Pradhan et al. for at least the reasons given above. Gonzalgo et al. fails to cure all of the deficiencies of Lopez et al. and Pradhan et al. with respect to claim 1. Therefore, based at least on its dependency from claim 1, claim 11 is patentable over the applied combination of Lopez et al., Pradhan et al. and Gonzalgo et al.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

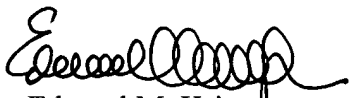
It is respectfully submitted that the present application is in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Kriegsman & Kriegsman

By: 

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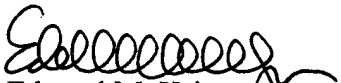

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